FORM PTO-1390 REV. 5-93	US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEYS DOCKET NUMBER P01,0235
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S.APPLICATION NO. (if known, see 37 CFR 1.5) **09/869839**

INTERNATIONAL APPLICATION NO. PCT/EP99/09756	INTERNATIONAL FILING DATE **30 November 1999**	PRIORITY DATE CLAIMED **5 January 1999**

TITLE OF INVENTION

CARDIAC PACEMAKER WITH ADJUSTABLE STIMULATION INTERVAL (AS AMENDED)

APPLICANT(S) FOR DO/EO/US

ROLAND HEINZE and KARL STANGL

pplicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay.
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of International Application as filed (35 U.S.C. 371(c)(2)) - drawings attached.
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2) -

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). Un-executed

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:
11.☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; (PTO 1449, Prior Art, Search Report).

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included. (Separate envelope)

13.☒ A FIRST preliminary amendment.
   ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☒ A substitute specification, including red-lined version

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information:
   a. ☒ Submission of drawings for Publication

   B ☒ Express Mail Label EL 843729535US

U.S.APPLICATION NO. (if known, see 37 C.F.R. 1.5) **09/869839**	INTERNATIONAL APPLICATION NO. PCT/EP99/09576	ATTORNEY'S DOCKET NUMBER P01,0235

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY

BASIC NATIONAL FEE (37 C.F.R. 1.492(a)(1)-(5):
Search Report has been prepared by the EPO or JPO $860.00

International preliminary examination fee paid to USPTO (37 C.F.R. 1.482) $690.00

No international preliminary examination fee paid to USPTO (37 C.F.R. 1.482) but international search fee paid to USPTO (37 C.F.R. 1.445(a)(2) $760.00

Neither international preliminary examination fee (37 C.F.R. 1.482) nor international search fee (37 C.F.R. 1.445(a)(2) paid to USPTO $1000.00

International preliminary examination fee paid to USPTO (37 C.F.R. 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00

	ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	

Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. 1.492(e)). | $ | |

Claims	Number Filed	Number Extra	Rate		
Total Claims	15 - 20 =	0	X $18.00	$	
Independent Claims	1 - 3 =	0	X $ 80.00	$	
Multiple Dependent Claims			$270.00 +	$	
		TOTAL OF ABOVE CALCULATIONS =		$860.00	

Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 C.F.R. 1.9, 1.27, 1.28) | $ | |

	SUBTOTAL =	$860.00	

Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).   + | $ | |

	TOTAL NATIONAL FEE =	860.00	

Fee for recording the enclosed assignment (37 C.F.R. 1.21(h). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). $40.00 per property   + | | |

	TOTAL FEES ENCLOSED =	$860.00	
		Amount to be refunded	$
		charged	$

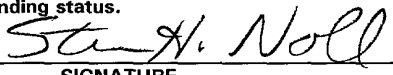a. ☒ A check in the amount of $860.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **501519** . A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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BOX PCT

IN THE UNITED STATES DESIGNATED OFFICE

OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER THE PATENT COOPERATION TREATY-CHAPTER II

5 **AMENDMENT "A" PRIOR TO ACTION AND SUBMISSION OF**

SUBSTITUTE SPECIFICATION

APPLICANT(S): Heinze et al.

ATTORNEY DOCKET NO. P01,0235

INTERNATIONAL APPLICATION NO: PCT/EP99/09756

10 INTERNATIONAL FILING DATE: November 30, 1999

INVENTION: "CARDIAC PACEMAKER WITH ADJUSTABLE STIMULATION INTERVAL" (AS AMENDED)

Assistant Commissioner for Patents

Washington, D.C. 20231

15 Sir:

Applicants herewith amend the above-referenced PCT application as follows, and request entry of the Amendment prior to examination in the United States National Examination Phase.

IN THE TITLE

20 Please cancel the present title and substitute the following title therefor:

--**CARDIAC PACEMAKER WITH ADJUSTABLE STIMULATION INTERVAL**--.

25 **IN THE SPECIFICATION:**

Please enter the substitute specification which is submitted herewith pursuant to 37 C.F.R. §1.125(b). A marked up copy showing all changes is also submitted herewith. The substitute specification does not contain any new matter.

IN THE CLAIMS:

Please cancel claims 1-13 and substitute the following claims therefor:

WE CLAIM AS OUR INVENTION

14.   A cardiac pacemaker comprising:

5   a pulse generator which emits stimulation pulses respectively separated by stimulation intervals, each having a stimulation interval duration and collectively having an average duration;

a lead connected to said pulse generator and adapted to deliver said stimulation pulses to a heart and to receive a signal containing

10   action potential information from the heart;

a modulation device connected to said pulse generator which alternatingly shortens and lengthens said stimulation interval duration without changing said average duration, thereby causing said pulse generator to emit modulated stimulation

15   pulses;

a detector connected to said lead to detect said signal after each modulated stimulation pulse, thereby producing a detector output;

an evaluation unit connected to said detector for analyzing said

20   detector output to determine an electric restitution of said heart at the average duration by measuring a duration of said action potential from said action potential information, said action potential duration having a measuring variable associated therewith, and for identifying a relationship between changes

25   in said measuring variable, caused by modulation of said stimulation interval, and said average duration, and for comparing said relationship to at least one predetermined value to obtain a comparison result; and

said modulation device for controlling said average duration

30   dependent on said comparison result.

15. A cardiac pacemaker as claimed in claim 14 wherein said modulation device operates at periodic intervals to cause said pulse generator to emit said modulated stimulation pulses.

16. A cardiac pacemaker as claimed in claim 14 wherein said modulation device operates continuously to cause said pulse generator to emit said modulation stimulation pulses.

17. A cardiac pacemaker as claimed in claim 14 wherein said measuring variable is selected from the group consisting of an actual duration of the action potential of the myocardium of the heart, a time interval between a modulated stimulation pulse and a following T wave, and a time interval between a QRS and a T wave each following a modulated stimulation pulse.

18. A cardiac pacemaker as claimed in claim 14 wherein said evaluation unit forms an average of said measuring variable over a plurality of stimulation intervals.

19. A cardiac pacemaker as claimed in claim 14 comprising storing said changes of said measuring variable over a plurality of change cycles.

20. A cardiac pacemaker as claimed in claim 14 wherein said evaluation unit, for identifying said change in said measuring variable, employs a dimensionless variable of said electric restitution.

21. A cardiac pacemaker as claimed in claim 20 wherein said evaluation unit employs a gradient of said electric restitution as said dimensionless variable, calculated by forming a quotient between a change of said measuring variable and a change of said stimulation interval caused by said modulation device.

22. A cardiac pacemaker as claimed in claim 21 wherein said predetermined value is selected dependent on said gradient during a resting state of a body in which said heart is disposed.

23.   A cardiac pacemaker as claimed in claim 20 wherein said evaluation unit, as said dimensionless variable, calculates a relative change in said electric restitution by forming a quotient between a change in said measuring variable and a previous value of said measuring variable.

24.   A cardiac pacemaker as claimed in claim 23 wherein said predetermined value is selected dependent on said relative change during a resting state of a body in which said heart is disposed.

25.   A cardiac pacemaker as claimed in claim 14 wherein said evaluation unit calculates an average value of said measuring variable over a plurality of stimulation intervals and wherein said average duration of said stimulation interval is fixed by external programming to a value obtained during a resting state of a body in which said heart is disposed, and wherein said fixed interval is stored as said predetermined value.

26.   A cardiac pacemaker as claimed in claim 25 further comprising a sensor which identifies said state of rest, and wherein said control unit causes said stored value of said stimulation interval to be used by said pulse generator during said state of rest.

27.   A cardiac pacemaker as claimed in claim 14 wherein said evaluation unit alters said predetermined value in dependence on a duration of said stimulation interval.

28.   A cardiac pacemaker as claimed in claim 14 wherein said evaluation unit operates said modulation unit to control said average duration by increasing said average duration if a difference between a gradient of said electric restitution and said predetermined value falls below a negative threshold value, and decreases said average duration if said difference exceeds a positive threshold value.

IN THE ABSTRACT:

Please add the Abstract as set forth on separately numbered page 18 attached hereto.

REMARKS:

The present Amendment makes editorial changes in the specification, and claims, and adds an Abstract, to bring the present PCT application into

5   conformity with the requirements of United States patent practice. The claims submitted herein are considered to be of the same scope as the original claims, and therefore the cancellation of original claims 1-13 is not considered by the Applicants as a surrender of any of the subject matter encompassed within the scope of those claims, and the claims

10   submitted herein are not considered to narrow any of the original claims.

Early consideration on the merits is therefore respectfully requested.

Submitted by,

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ABSTRACT

A cardiac pacemaker has a pulse generator which emits stimulation pulses which are respectively separated by stimulation intervals and which collectively have an average duration. A modulation device alternatingly shortens and lengthens the stimulation intervals, without changing the average duration. An evaluation unit analyzes signals detected after each stimulation pulse and determines the electric restitution of the heart at the average stimulation interval duration on the basis of a measurement of the duration of the action potential. Changes in a measuring variable, associated with the duration of the action potential, caused by the modulation of the stimulation intervals is determined in a relationship to the average duration of the stimulation interval. This relationship is compared with at least one predetermined value, and the average duration of the stimulation interval is controlled on the basis of this comparison.

<u>SUBSTITUTE SPECIFICATION</u>

S P E C I F I C A T I O N

TITLE

"CARDIAC PACEMAKER WITH ADJUSTABLE STIMULATION INTERVAL"

<u>BACKGROUND OF THE INVENTION</u>

<u>Field of the Invention</u>

5   The present invention is directed to a cardiac pacemaker, and in particular to a cardiac pacemaker wherein the stimulation interval between stimulation pulses is adjustable.

<u>Description of the Prior Art</u>

10   A generally known cardiac pacemaker is the so-called QT-or stimulus-T pacemaker such as is described for example in United States Patent No. 4,228,803. Such a pacemaker has means with which the median stimulation frequency can be adapted to changes in physical and psychic stress.

To this end a circuit is provided which evaluates the ECG signal

15   derived intracardially, detecting the beginning or the maximum of the T wave. Since the time interval between stimulation and the start of the T wave, the so-called stim-T interval shortens with increasing stress, the circuit delivers a physiological measuring parameter with which the stimulation frequency can be adapted to changing stresses.

20   The principle disadvantage of a frequency control system of this kind is due to the fact that the stim-T interval does not shorten only with an increase in stress, but shortens to a considerably greater degree through the rise of the stimulation frequency itself.   Frequency control of this type

correspondingly requires special measures in order to avoid positive feedback.

A further disadvantage of this system of frequency control is the fact that the measured stim-T intervals are dependent on hormonal secretions, i.e., they respond to hormones secreted by the adrenal cortex and transported via the blood circulation.

In principle, in the regulation of the stimulation frequency in cardiac pacemakers it is an essential goal to adapt the stimulation frequency not only to rising physical stresses, but also to take into account the individual myocardial capacity of the patient. This means that the stimulation frequency is increased with rising stress only as long as a rise in the heart time volume (HTV) is achieved. This is intended to prevent the myocardium from being overloaded and damaged by too high a stimulation frequency ("overpacing").

An attempt has been made to achieve this control by measuring the beat volume BV or an HTV-dependent measuring parameter, such as for example the central venous oxygenation (s02).

From PCT Application WO 89/06990 a method is known for hemodynamic optimization of the stimulation frequency, which uses the measurement of the central venous oxygenation s02, dependent on the heart time volume, in combination with a modulation of the stimulation frequency ΔHR over phases of two to four minutes. Optimization of the heart time volume is sought in that the frequency-dependent gradient of the

oxygenation AsO2/ΔHR is kept within a predetermined range, which is a physiologically optimum range analogous to the gradient of the heart time volume HTV/ΔHR.

This method depends on the stability and the accuracy of the s02 sensor catheter, which in practice have not proved to be sufficient, and the method has the disadvantage that on account of the necessary long change periods it is not possible in the necessary time of a few minutes to differentiate whether the measured s02 change is caused by the frequency change or by other influencing variables.

European Application 0 551 355 describes a method for modulating individual stimulation intervals in which the impedance measurement is used to detect the beat volume, in order to avoid the use of a sensor catheter to determine the heart time volume. Through the deliberate modulation of individual stimulation intervals ΔSI and the phase- specific demodulation of the impedance change ΔZ, an attempt was made to suppress the influence of non- function-specific and thus disturbing parameter changes, and in addition the signal was calibrated with the aid of maximum modulation.

This method has the disadvantage that the principle of modulating individual stimulation intervals here is only used as a filtering and calibration method, i.e. as an interim step to determine the beat volume and thus the heart time volume (HTV). Optimization of the frequency control is then also sought by the optimization of the gradient ΔHTV/ΔHR on the basis of an optimum hemodynamic characteristic curve. The determination of the beat

volume, despite an improvement in the signal-to-noise-ratio as a result of the individual pulse modulation, has in practice still proved too inaccurate to be able to carry out reliable hemodynamic optimization. This means that optimization of the stimulation by controlling the heart time volume has in

5   practice been problematic, since either the specific sensor catheters for measuring the beat volume or the HTV-dependent measuring parameters still have no adequate long-term stability, or measurements of the beat volume using standard catheters via the impedance are not sufficiently reliable. Moreover the evaluation becomes very complex since the

10   mechanical transmission functions also detected and which falsify the measuring result must also be taken into account.

SUMMARY OF THE INVENTION

An object of the invention is to provide a cardiac pacemaker which renders possible quick and accurate regulation of the stimulation frequency

15   or respectively of the duration of the stimulation interval, and overloading by too high a stimulation frequency is avoided.

The above object is achieved in accordance with the invention in a cardiac pacemaker having a pulse generator which emits stimulation pulses respectively separated by stimulation pulses respectively separated by

20   stimulation intervals, each having a stimulation interval duration, and which collectively have an average duration, and a lead connected to the pulse generator which is adapted to deliver the stimulation pulses to a heart as well as to receive a signal containing action potential information from the heart,

a modulation device connected to the pulse generator which alternatingly shortens and lengthens the stimulation interval without change the average duration, thereby cause the pulse generator to emit modulated stimulation pulses, a detector connected to the lead to detect the signal received from the heart after each modulated stimulation pulse, and an evaluation unit connected to the detector for analyzing the detector output therefrom. The evaluation unit determines the electric restitution of the heart at the average stimulation interval duration by measuring the duration of the action potential in the detector output. The evaluation unit selects a measuring variable associated with the action potential duration and identifies changes in the measuring variable caused by modulation of the stimulation intervals, relative to the average duration of the stimulation intervals, and compares the relationship between the measuring variable and the average duration to at least one predetermined value. Dependent on the result of this comparison, the average duration of the stimulation interval is controlled.

The cardiac pacemaker according to the invention which has an individually optimized regulation of the duration of the stimulation interval, avoids the necessity of determining a BV- or HTV-dependent measuring parameter and makes possible, through evaluation of the electric restitution or of the gradient of the electric restitution with the aid of the standard detection of the endocardiac ECG, a regulation of the stimulation frequency or of the duration of the stimulation interval by means of a function parameter of the heart, which directly reproduces the stress state of the

patient, changes in the capacity of the myocardium and acute worsening of myocardial performance being taken into account in the frequency adaptation. Here the modulation of individual stimulation intervals is carried out in such a way that the average adjusted interval duration does not change.

The modulation of the stimulation intervals by a positive value and a negative value is carried out continuously as well as at an interval of a number of pulses with periodic repetition.

It was found that the electric restitution curve which is determined by measuring the duration of action potential, is equivalent to that which is defined by measuring the QT or the stim-T interval of the electrocardiogram.

Furthermore it has been shown that the analysis of the load- and frequency-dependent modulation of the stim-T interval is sufficiently reliable if the modulation of an individual stimulation interval gives the20inequations ESI (Extrasystolic Interval) <600ms with ΔESI/BCL $\geq$10% (BCL = basic cycle length).

As the evaluation variable of the electric restitution, (advantageously a dimensionless variable), the gradient (ERG) or the relative change in the electric restitution can be used, for example, in order to achieve load-dependent control. This is possible because this gradient coincides with the rise in the physical load, while it rises with increasing stimulation frequency. Moreover it was also found that the change reaction is based mainly on a change in the time constants of the exponential restitution function and this

time constant reacts substantially more quickly and more strongly to changes in the load and the frequency than does the stim-T interval in a control system according to the prior art.

Furthermore the control system according to the invention can be used well in cases of acute ischemia since the electric restitution reflects the myocardial conditions. The time constant of the exponential electric restitution, and also the gradient of same, rises with the ischemia. According to the invention this causes a reduction in the stimulation frequency.

The control system according to the invention using a single pulse modulation and detection of the electric restitution causes a quick and accurate regulation of the stimulation frequency, since the electric restitution is controlled mainly by a quick reaction mechanism controlled by neurons.

DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the characteristic course of an electric restitution curve of a normal healthy myocardium in a resting phase and in a load phase.

Fig. 2 shows characteristic curves for the electric restitution gradient as a function of the stimulation frequency in the rest phase and the load phase.

Fig. 3 shows characteristic curves of the gradient of the electric restitution dependent on the stimulation frequency given the occurrence of ischemia.

Fig. 4 is a block diagram of an embodiment of a cardiac pacemaker constructed and operating in accordance with the principles of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

5   The dependence of the duration of the action potential 5 AP of the myocardium as a function parameter of the duration of the diastole t_d is designated as electric restitution. If this is spontaneously changed during a single heart cycle, for example through an extrasystole, then the action potential or its duration changes. The duration of the action potential is defined by the interval between the beginning of the stimulation and the time at which the action potential has sunk by 90%, and it decreases if the time interval between two successive stimulation pulses becomes smaller. Here a distinction is to be made between the APD change after an extrasystolic stimulation interval and the APD change after a change in the median or basic heart frequency (HR = 1 BCL) according to prior art.

This alteration behavior after an extrasystolic stimulation interval can be described by a double exponential function which is referred to as the electric restitution curve ER.

The electric restitution curve (ERC) is thus defined as 25 a function of the action potential duration APD of the cycle length of a previous extrasystolic stimulation pulse interval ESI, i.e. of an individual stimulation pulse interval which is changed from the basic cycle length (BCL), i.e. the

median stimulation interval duration by $\pm\Delta ESI$, and which corresponds to the diastole.

The function can be described as

$$ER\ APD(ESI) = APD_{p1}(1-A1*exp(\sim t_d/T1)-A2*exp(-t_d/T2)\ ).$$

5   Herein, APD_{p1} is the plateau value, A1 and T1 are the amplitude and time constant of the quick phase of the restitution and A2 and T2 are the amplitude and time constant of the slow phase of the restitution.

The distinction in the approximate equation between a slow and a quick portion in the exponential rise of the restitution curve takes into

10   account the fact that functions of the myocardium or of the myocardial cell are determined at the cell membrane like the ion exchange, i.e. both through quick autonomous regulating processes in the cell and the surrounding tissue and also through regulating processes which affect the whole heart-cardiovascular system and are controlled by the sympathetic nervous system

15   and the corresponding gland functions.

As a measuring parameter to determine the electric restitution curve, as indicated above, in principle the action potential duration APD is determined which can be measured by special electrodes. Tests have shown however that in measuring the ECG also the so-called QT interval, i.e.

20   the duration of the interval between the Q peak and the end of the T wave of the intracardiac ECG has the same restitution characteristic as the APD. When stimulating the ventricle with a cardiac pacemaker 25 it is more expedient to measure, instead of the QT interval as the measuring interval,

the stim-T interval STI, i.e. the interval between stimulation pulse and T wave.

Fig. 1 shows, as the electrical restitution 30 curve (continuous line), the course of the action potential duration APD in dependence on the length of individual extrasystolic intervals of a normal healthy myocardium for the rest phase and for a load phase. Here in both phases respectively the optimum adapted stimulation frequency HRo or the optimum basic cycle length BCLo =1/HRo (i.e. the median duration of the stimulation interval) was changed in individual extrasystolic stimulation intervals ESI and then the corresponding change in the action potential duration APD was measured. The restitution curves thus produced correspond to the exponential functions described by the above equation. The optimum basic cycle length BCLo for rest (90 ms) and for a load (500 ms) are represented by the broken arrows, i.e. the respective basic cycle length or median interval duration was altered by $\pm\Delta$ESI to form extrasystolic intervals, and respectively as the reaction the action potential duration or the QT- or stim-T interval was measured as the measuring parameter. Here mean durations of the stimulation interval were alternately so shortened and prolonged by positive and negative ΔESI values that the adjusted average interval duration remains the same. Preferably the $\pm\Delta$ESI remains the same during a change, i.e. the interval duration is shortened and prolonged by the same value. The change can be repeated periodically at an interval of a number of pulses, however it can also be

carried out continuously, i.e. each stimulation pulse is alternately shortened or prolonged.

The broken lines in Fig. 1 represent the curves of the QT or stim-T intervals of an ECG with continuous alteration of the basic cycle length, or respectively with continuous modulation, which is used for example in a QT pacemaker according to prior art. As can be recognized, these characteristic curves are clearly different from the electric restitution curves with a differing load, and with increasing load, in addition to a reduction of the plateau value of the respective curve with a corresponding displacement to the left also a steeper rise in the curve was measured.

The restitution curve can now be used for physiological control of the stimulation frequency HR, it being essential, as mentioned, that both the plateau value APD_{p1} and the time constants T1 and T2 are dependent on the pulse frequency HR and the level of myocardial efficiency. The stimulation frequency should therefore be so adjusted that the stimulation interval lies in the region of the plateau value APD_{p1} with any load.

In order to be able to use a simpler variable for the 10 regulation, advantageously not directly the region around the plateau value itself is selected but the gradient of the restitution curve. The gradient of the restitution curve in the respective optimum operating point, which is given by the optimum basic cycle length BCLo arises in that the extrasystolic interval ESI is altered as a percentage (ΔESI/BOL) by a defined positive +ΔESI and/or negative value -ΔESI and the resulting change in the action potential

duration $+\Delta APD$ or $-\Delta APD$, shown by arrows 20 in Fig. 1, is measured. If this gradient of the electric restitution ERG $= +\Delta APD/+\Delta ESI$ or ERG $= -\Delta APD/-\Delta ESI$ is applied as a function of the stimulation frequency HR for the rest phase and a load phase, the course represented in Fig. 2 arises.

5   Fig. 2 shows that the exponential rise of the gradient of the electric restitution ERG as a function of a rising stimulation frequency HR with rising load is displaced to the right. It can be recognized that in the respective optimum heart frequency, the associated ERGo values, which correspond to the plateau values APD_{p1} in Fig. 1, have approximately the same level,

10   however the values can also be different. These values can be selected in a frequency control system as set values of the gradient of the electric restitution ERG, a region around the set value ERG being given in Fig. 2 as a range for an optimum stimulation frequency HR, which is delimited by the threshold values ERG1 and ERG2.

15   It is also conceivable that the gradient of the electric restitution ERG is determined from the difference between the positive and negative changes in the action potential duration in relation to the positive and negative interval changes, namely with $ERG[(+\Delta APD)-(-\Delta APD)]/\{(+\Delta ESI)-(-\Delta ESI)]$.

On the basis of Figs. 1 and 2 it can be recognized that the electric

20   restitution function or its gradient ERG offers the precondition for regulating the stimulation frequency since the gradient of the electric restitution ERG reacts with an increase in the stimulation frequency conversely to the rise in the physical stress, and has within a physiologically fixed defined region an

optimum value ERGo for each stress situation. From the ERG characteristic curve according to Fig. 2 it can be recognized that in the frequency control too high a stimulation frequency (overpacing) is avoided in principle.

However it is also apparent that a possible acute worsening in myocardial performance in patients can occur and can be taken into account in the adaptation of the frequency. In Fig. 3 is represented the gradient of the electric restitution via the stimulation frequency for a case in which a worsening of the myocardial performance occurs through ischemia. Fig. 3 shows that the lengthening of the stim-T interval on the occurrence of an ischemia displaces the ERG curve to the left in a case of stress, i.e. the gradient of the electric restitution reacts on a drop in the myocardial capacity as in a drop in physical stress. As a result of this, the optimum stimulation frequency PRo is reduced and thus the pre-eminent requirement is met that the ERG-dependent frequency control system prevents overpacing in a myocardium which is deteriorating pathologically.

In another example, instead of the gradient, the relative change in the electric restitution can be used by forming the quotient $\Delta APD/\Delta ESI$, in each case also the median values being able to be determined over a plurality of change cycles.

In Fig. 4 is represented an embodiment of a cardiac 10 pacemaker, with which frequency control is used in dependence on the gradients of the electric restitution function ERG.

The functional blocks required for controlling frequency or the stimulation interval in dependence on the ERG are represented in the bordered area. As other functional blocks, which form part of the standard equipment of a normal QT pacemaker, a stimulation electrode 1 and a

5	stimulation pulse generator supplying the stimulation electrode 1 are provided. Furthermore an ECG amplifier 2 is connected on the one hand to the stimulation electrode 1 and on the other hand to a detection stage for detecting the stim-T interval as a measuring variable. Moreover such a system contains a microprocessor, which can be programmed via a

10	telemetry 25 stage 12, with a process control 11.

The functional blocks of the frequency control system are an HRmax/HRmin memory 7 to store the limit values of the stimulation frequency, a control stage 8 connected to the memory, to which stage a control variable ΔERG is supplied, a stimulation interval modulator 9 to fix

15	and modulate the stimulation interval and which is connected to the stimulation pulse generator 10. Furthermore a calculation stage 4 is provided which receives a signal from the detection stage 3 and from the modulator 9, and a stage 5 to form the average value, a set value memory 6 and a set/actual value comparator 13.

20	The functioning of the cardiac pacemaker is as follows. 5 The stimulation pulse generator 10 supplies a stimulation pulse to the stimulation electrode and the ECG amplifier amplifies the intracardial ECG signal derived via the stimulation electrode 1. From this amplified signal, the

detection stage 3 analyses the interval duration STI between the stimulation pulse and the T wave which corresponds to the QT interval or the action potential duration. In the calculation stage 4, the gradient of the electric restitution ERG is calculated, however others of the above-mentioned variables can also be used. To this end first of all, triggered by the modulator 9, the change $\pm\Delta$STI is calculated, with the stim-T interval value supplied by the detection stage, which change has been caused by the change ΔESI in the stimulation interval, and then the quotient ERG = ΔSTI/ΔESI is determined. In the median value stage 5, the median value ERGm of the ERG values is calculated over a plurality of change cycles. With the arrow from the exit of the median value stage 5 to the set value memory 6 is indicated that the ERGm value, which in the body's rest state is measured at a median stimulation frequency of roughly 90/min, is stored as the set value.

In the set Value/actual Value Comparator 13, the difference between the median value of the gradient of the electric restitution ERGm and the set value ERGs is formed, and is given as the difference value ΔERG to the control stage 8, the latter being used to adjust the median stimulation frequency HR_0. This is calculated for example with the aid of the following functions:

$HR_0 = HR_{min} + k*\Delta ERG$,

wherein HR is so regulated that HR is < HRmax. Here HRmin and HRmax are minimum or maximum frequencies which can be predetermined by

external programming and stored in the memory 7, and k is a proportionality

factor. HRmin is generally predetermined by the optimum median stimulation

frequency HRo in the rest state. The basic frequency HRo thus determined

is supplied to the modulation stage 9, in which the basic cycle length BOL =

5   1/HRo is modulated periodically with an interval change $\pm\Delta$ESI and the

resulting stimulation interval ESI = BCLo + ΔESI is formed. In the following

stimulation pulse generator 10, the stimulation pulse is then output in

dependence on the ESI value. The regulation is repeated until the value

ΔERG is zero.

10   In the above-described value, as the set value for the gradient of the

electric restitution ERGs, the level was selected which arises for the

individual load curves according to Fig. 2 at the optimum stimulation

frequency HRo, control fluctuations between the values ERG1 and ERG2

being admitted. The set value ERGs can however also be automatically

15   adapted to longer-term fluctuations of the restitution gradient with the aid of

a second measuring parameter, independent of the modulation, with which

parameter it is possible to recognize the rest state of the patient. In the rest

phase then the minimum stimulation rate HRmin is automatically adjusted

and the set value ERGs is adapted to the restitution gradient measured at

20   rest. In this manner, the set value is "recalibrated". The measuring

parameter which is independent of the modulation can be supplied for

example by a mechanical movement sensor. The set value can also be

adjusted in dependence on the frequency, for example it can be fixed during the rest state and then provided with a frequency-dependent slope.

Although modifications and changes may be suggested by those skilled in the art, it is the intention of the inventors to embody within the patent warranted hereon all changes and modifications as reasonably and properly come within the scope of their contribution to the art.

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[PCT/EP99/09756

St. Jude Medical AB

99P2001P

Cardiac pacemaker

5   The Invention relates to a cardiac pacemaker in accordance with the preamble of the main claim.]

--S P E C I F I C A T I O N
TITLE
"CARDIAC PACEMAKER WITH ADJUSTABLE STIMULATION INTERVAL"

10   ### BACKGROUND OF THE INVENTION
Field of the Invention

The present invention is directed to a cardiac pacemaker, and in particular to a cardiac pacemaker wherein the stimulation interval between stimulation pulses is adjustable.

15   ### Description of the Prior Art--

A generally known cardiac pacemaker is the so-called QT-or stimulus-T pacemaker such as is described for example in [US 422 8 803] United States Patent No.4,228,803. Such a pacemaker has means with which the median stimulation frequency can be adapted to changes in physical and

20   psychic stress.

To this end a circuit is provided which evaluates the ECG signal derived intracardially, detecting the beginning or the maximum of the T wave. Since the time interval between stimulation and the start of the T wave, the so-called stim-T interval shortens with increasing stress, the circuit delivers

a physiological measuring parameter with which the stimulation frequency can be adapted to changing stresses.

The principle disadvantage of a frequency control system of this kind is [given in] <u>due to the fact</u> that the stim-T interval does not shorten only with

5   an increase in stress<u>,</u> but <u>shortens</u> to a considerably greater degree through the rise of the stimulation frequency itself. Frequency control of this type correspondingly requires special measures in order to avoid positive feedback.

A further disadvantage of this system of frequency control is the fact

10   that the measured stim-T intervals are <u>dependent on hormonal secretions,</u> <u>i.e., they respond to</u> [determined from humours i.e. react on the basis of the] hormones [poured out via] <u>secreted by</u> the adrenal cortex and transported via the blood circulation.

In principle, in the regulation of the stimulation frequency in cardiac

15   pacemakers it is an essential goal to adapt the stimulation frequency not only to rising physical stresses, but [in so doing] also to take into account the individual myocardial capacity of the patient. This means that the stimulation frequency is [only] increased with rising stress <u>only</u> as long as [thereby] a rise in the heart time volume (HTV) is achieved. This is intended to prevent the

20   myocardium from being overloaded and damaged by too high a stimulation frequency ("overpacing").

An attempt has been made to achieve this control by measuring the beat volume BV or an HTV-dependent measuring parameter, such as for example the central venous oxygenation (s02).

From PCT Application WO 89/06990 [is known] a method is known

5   for hemodynamic optimization [haemodynamic optimisation] of the stimulation frequency, which uses the measurement of the central venous oxygenation s02, dependent on the heart time volume, in combination with a modulation of the stimulation frequency ΔHR over phases of two to four minutes. [Optimisation] Optimization of the heart time volume is [aimed at]

10   sought in that the frequency-dependent gradient of the oxygenation AsO2/AHR is kept within a predetermined range, which is a physiologically optimum range analogous to the gradient of the heart time volume HTV/ΔHR.

This method depends on the stability and the accuracy of the s02

15   sensor catheter, which in practice have not proved to be sufficient, and the method has the disadvantage that on account of the necessary long change periods it is not possible in the necessary time of a few minutes to differentiate whether the measured s02 change is caused by the frequency change or by other influencing variables.

20   [EP] European Application 0 551 355 describes a method for modulating individual stimulation intervals in which the impedance measurement is used to detect the beat volume, in order to avoid the use of a sensor catheter to determine the heart time volume. Through the

deliberate modulation of individual stimulation intervals ΔSI and the phase-specific demodulation of the impedance change ΔZ, an attempt was made to suppress the influence of non- function-specific and thus disturbing parameter changes, and in addition the signal was calibrated with the aid of

5   maximum modulation.

This method has the disadvantage that the principle of modulating individual stimulation intervals here is only used as a filtering and calibration method, i.e. as an interim step to determine the beat volume and thus the heart time volume (HTV). [Optimisation] Optimization of the frequency

10   control is then also [aimed at] sought by the [optimisation] optimization of the gradient AHTV/ΔHR on the basis of an optimum [haemodynamic] hemodynamic characteristic curve. The determination of the beat volume, despite an improvement in the signal—to-noise-ratio as a result of the individual pulse modulation, has in practice still proved too inaccurate to be

15   able to carry out reliable [haemodynamic optimization] hemodynamic optimization. This means that [optimisation] optimization of the stimulation by controlling the heart time volume [presents itself] has in practice [as] been problematic, since either the specific sensor catheters Sfor measuring the beat volume or the HTV—dependent measuring parameters still have no

20   adequate long—term stability, or measurements of the beat volume using standard catheters via the impedance are not sufficiently reliable. Moreover the evaluation becomes very complex since the mechanical transmission

functions also detected and which falsify the measuring result must also be taken into account.

SUMMARY OF THE INVENTION

[The] An object [underlying] of the invention is to [create] provide a

5   cardiac pacemaker which renders possible quick and accurate regulation of the stimulation frequency or respectively of the duration of the stimulation interval, and overloading by too high a stimulation frequency is avoided.

The above object is achieved in accordance with the invention in a cardiac pacemaker having a pulse generator which emits stimulation pulses

10   respectively separated by stimulation pulses respectively separated by stimulation intervals, each having a stimulation interval duration, and which collectively have an average duration, and a lead connected to the pulse generator which is adapted to deliver the stimulation pulses to a heart as well as to receive a signal containing action potential information from the heart,

15   a modulation device connected to the pulse generator which alternatingly shortens and lengthens the stimulation interval without change the average duration, thereby cause the pulse generator to emit modulated stimulation pulses, a detector connected to the lead to detect the signal received from the heart after each modulated stimulation pulse, and an evaluation unit

20   connected to the detector for analyzing the detector output therefrom. The evaluation unit determines the electric restitution of the heart at the average stimulation interval duration by measuring the duration of the action potential in the detector output. The evaluation unit selects a measuring variable

associated with the action potential duration and identifies changes in the measuring variable caused by modulation of the stimulation intervals, relative to the average duration of the stimulation intervals, and compares the relationship between the measuring variable and the average duration to at least one predetermined value. Dependent on the result of this comparison, the average duration of the stimulation interval is controlled.

The cardiac pacemaker according to the invention which has an individually [optimised] optimized regulation of the duration of the stimulation interval, avoids the necessity of determining a BV- or HTV-dependent measuring parameter and makes possible, through evaluation of the electric restitution or of the gradient of the electric restitution with the aid of the standard detection of the endocardiac FOG, a regulation of the stimulation frequency or of the duration of the stimulation interval by means of a function parameter of the heart, which directly reproduces the stress state of the patient, changes in the capacity of the myocardium and acute worsening of myocardial performance being taken into account in the frequency adaptation. Here the modulation of individual stimulation intervals is carried out in such a way that the [median] average adjusted interval duration does not [alter] change.

[Through the measures quoted in the subordinate claims, advantageous developments and improvements are possible.]

The modulation of the stimulation intervals by a positive value and a negative value is carried out [both] continuously [and also] <u>as well as</u> at an interval of a [plurality] <u>number</u> of pulses with periodic repetition.

It was found that the electric restitution curve which is determined by measuring the duration of action potential, is equivalent to that which is defined by measuring the QT or the stim-T interval of the electrocardiogram.

Furthermore it has been shown that the analysis of the load- and frequency-dependent modulation of the stim-T interval is sufficiently reliable if the modulation of an individual stimulation interval gives the20inequations ESI (Extrasystolic Interval) <600ms with $_\Delta$ESI/BCL $\geq$ 10% (BCL = basic cycle length).

As the evaluation variable of the electric restitution, (advantageously a dimensionless variable) [e.g.] the gradient (ERG) or the relative change in the electric restitution can be used, for example, in order to achieve load-dependent control. This is possible [since] <u>because</u> this gradient coincides with the rise in the physical load, [whilst] <u>while</u> it rises with increasing stimulation frequency. Moreover it was also found that the change reaction is based mainly on a change in the time constants of the exponential restitution function and this time constant reacts substantially more quickly and more strongly to changes in the load and the frequency than does the stim-T interval in a control system according to <u>the</u> prior art.

Furthermore the control system according to the invention can be used well in cases of acute ischemia since the electric restitution reflects the

myocardial conditions. The time constant of the exponential electric restitution, and also the gradient of same, rises with the ischemia. According to the invention this causes a reduction in the stimulation frequency.

5
The control system according to the invention using a single pulse modulation and detection of the electric restitution causes a quick and accurate regulation of the stimulation frequency, since the electric restitution is controlled mainly by a quick reaction mechanism controlled by neurons.

[An embodiment of the invention is represented in the drawing and is described in greater detail in the following description.

10
The figures show:

Fig. 1 the characteristic course of an electric restitution curve of a normal healthy myocardium for the rest and for the load phase,

Fig. 2 characteristic curves for the electric restitution gradient as a function of the stimulation frequency in the rest phase and the load phase,

15
Fig. 3 characteristic curves of the gradient of the electric restitution in dependence on the stimulation frequency on occurrence of an ischemia and

Fig. 4 a block diagram of an embodiment of the cardiac pacemaker according to the present invention.]

20
DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the characteristic course of an electric restitution curve of a normal healthy myocardium in a resting phase and in a load phase.

Fig. 2 shows characteristic curves for the electric restitution gradient as a function of the stimulation frequency in the rest phase and the load phase.

Fig. 3 shows characteristic curves of the gradient of the electric restitution dependent on the stimulation frequency given the occurrence of ischemia.

Fig. 4 is a block diagram of an embodiment of a cardiac pacemaker constructed and operating in accordance with the principles of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The dependence of the duration of the action potential 5 AP of the myocardium as a function parameter of the duration of the diastole td is designated as electric restitution. If this is spontaneously changed during a single heart cycle, for example through an extrasystole, then the action potential or its duration changes. The duration of the action potential is defined by the interval between the beginning of the stimulation and the time at which the action potential has sunk by 90%, and it decreases if the time interval between two successive stimulation pulses becomes smaller. Here a distinction is to be made between the APD change after an extrasystolic stimulation interval and the APD change after a change in the median or basic heart frequency (HR = 1 BCL) according to prior art.

This alteration [behaviour] <u>behavior</u> after an extrasystolic stimulation interval can be described by a double exponential function which is referred to as the electric restitution curve ER.

The electric restitution curve (ERC) is thus defined as 25 a function of the action potential duration APD of the cycle length of a previous extrasystolic stimulation pulse interval ESI, i.e. of an individual stimulation pulse interval which is changed from the basic cycle length (BCL), i.e. the median stimulation interval duration by $\pm\Delta$ESI, and which corresponds to the diastole.

The function can be described as

$$ER\ APD(ESI) = APD_{p1}(1-A1*exp(\sim t_d/T1)-A2*exp(-t_d/T2)\ ).$$

Herein, APD_{p1} is the plateau value, A1 and T1 are the amplitude and time constant of the quick phase of the restitution and A2 and T2 are the amplitude and time constant of the slow phase of the restitution.

The distinction in the approximate equation between a slow and a quick portion in the exponential rise of the restitution curve takes into account the fact that functions of the myocardium or of the myocardial cell are determined at the cell membrane like the ion exchange, i.e. both through quick autonomous regulating processes in the cell and the surrounding tissue and also through regulating processes which affect the whole heart-cardiovascular system and are controlled by the [vegetative] <u>sympathetic</u> nervous system and the corresponding gland functions.

As a measuring parameter to determine the electric restitution curve, as indicated above, in principle the action potential duration APD is determined which can be measured by special electrodes. Tests have shown however that in measuring the ECG also the so-called QT interval, i.e.

5   the duration of the interval between the Q peak and the end of the T wave of the intracardiac ECG has the same restitution characteristic as the APD. [On] When stimulating the ventricle with a cardiac pacemaker 25 it is more expedient to measure, instead of the QT interval as the measuring interval, the stim-T interval STI, i.e. the interval between stimulation pulse and T

10 wave.

[In] Fig. 1 [is represented] shows, as the electrical restitution 30 curve (continuous line), the course of the action potential duration APD in dependence on the length of individual extrasystolic intervals of a normal healthy myocardium for the rest phase and for a load phase. Here in both

15 phases respectively the optimum adapted stimulation frequency HRo or the optimum basic cycle length BCLo =1/HRo (i.e. the median duration of the stimulation interval) was changed in individual extrasystolic stimulation intervals ESI and then the corresponding change in the action potential duration APD was measured. The restitution curves thus produced

20 correspond to the exponential functions described by the above equation. The optimum basic cycle length BCLo for rest (90 ms) and for a load (500 ms) are represented by the broken arrows, i.e. the respective basic cycle length or median interval duration was altered by ±ΔESI to form extrasystolic

intervals, and respectively as the reaction the action potential duration or the QT- or stim-T interval was measured as the measuring parameter. Here mean durations of the stimulation interval were alternately so shortened and prolonged by positive and negative ΔESI values that the adjusted [median] average interval duration remains the same. Preferably the $\pm$AESI remains the same during a change, i.e. the interval duration is shortened and prolonged by the same value. The change can be repeated periodically at an interval of a [plurality] number of pulses, however it can also be carried out continuously, i.e. each stimulation pulse is alternately shortened or prolonged.

The broken lines in Fig. 1 represent the curves of the QT or stim-T intervals of an ECG with continuous alteration of the basic cycle length, or respectively with continuous modulation, which is used for example in a QT pacemaker according to prior art. As can be [recognised], recognized these characteristic curves are clearly different from the electric restitution curves with a differing load, and with increasing load, in addition to a reduction of the plateau value of the respective curve with a corresponding displacement to the left also a steeper rise in the curve was measured.

The restitution curve can now be used for physiological control of the stimulation frequency HR, it being essential, as mentioned, that both the plateau value APD_{p1} and the time constants T1 and T2 are dependent on the pulse frequency HR and the level of myocardial efficiency. The stimulation

frequency should therefore be so adjusted that the stimulation interval lies in the region of the plateau value APD_{p1} with any load.

In order to be able to use a simpler variable for the 10 regulation, advantageously not directly the region around the plateau value itself is

5   selected but the gradient of the restitution curve. The gradient of the restitution curve in the respective optimum operating point, which is given by the optimum basic cycle length PCLo arises in that the extrasystolic interval ESI is altered as a percentage ($\Delta ESI/BOL$) by a defined positive $+\Delta ESI$ and/or negative value $-\Delta ESI$ and the resulting change in the action potential

10   duration $+\Delta APD$ or $-\Delta APD$, shown by arrows 20 in Fig. 1, is measured. If this gradient of the electric restitution ERG = $+\Delta APD/+\Delta ESI$ or ERG = $-\Delta APD/-\Delta ESI$ is applied as a function of the stimulation frequency HR for the rest phase and a load phase, the course represented in Fig. 2 arises.

Fig. 2 shows that the exponential rise of the gradient of the electric

15   restitution ERG as a function of a rising stimulation frequency HR with rising load is displaced to the right. It can be [recognised] <u>recognized</u> that in the respective optimum heart frequency, the associated ERGo values, which correspond to the plateau values APD_{p1} in Fig. 1, have approximately the same level, however the values can also be different. These values can be

20   selected in a frequency control system as set values of the gradient of the electric restitution ERG, a region around the set value ERG being given in Fig. 2 as a range for an optimum stimulation frequency HR, which is delimited by the threshold values ERG1 and ERG2.

It is also conceivable that the gradient of the electric restitution ERG is determined from the difference between the positive and negative changes in the action potential duration in relation to the positive and negative interval changes, namely with ERG[(+ΔAPD)-(-ΔAPD)]/{(+ΔESI)-(-ΔESI)].

5   On the basis of Figs. 1 and 2 it can be [recognised] <u>recognized</u> that the electric restitution function or its gradient ERG offers the precondition for regulating the stimulation frequency since [on the one hand] the gradient of the electric restitution ERG reacts with an increase in the stimulation frequency conversely to the rise in the physical stress, and [on the other

10   hand] has within a physiologically fixed defined region an optimum value ERGo for each stress situation. From the ERG characteristic curve according to Fig. 2 it can be [recognised] <u>recognized</u> that in the frequency control too high a stimulation frequency (overpacing) is avoided in principle.

However it is also apparent that a possible acute worsening in

15   myocardial performance in patients can [be recognised] <u>occur</u> and can be taken into account in the adaptation of the frequency. In Fig. 3 is represented the gradient of the electric restitution via the stimulation frequency for a case in which a worsening of the myocardial performance occurs through ischemia. Fig. 3 shows that the lengthening of the stim-T

20   interval on the occurrence of an ischemia displaces the ERG curve to the left in a case of stress, i.e. the gradient of the electric restitution reacts on a drop in the myocardial capacity as in a drop in physical stress. As a result of this, the optimum stimulation frequency PRo is reduced and thus the pre-eminent

requirement is met that the ERG-dependent frequency control system prevents overpacing in a myocardium which is deteriorating pathologically.

In another example, instead of the gradient, the relative change in the electric restitution can be used by forming the quotient $\Delta APD/\Delta ESI$, in each case also the median values being able to be determined over a plurality of change cycles.

In Fig. 4 is represented an embodiment of a cardiac 10 pacemaker, with which frequency control is used in dependence on the gradients of the electric restitution function ERG.

The functional blocks required for controlling frequency or the stimulation interval in dependence on the ERG are represented in the bordered area. As other functional blocks, which form part of the standard equipment of a normal QT pacemaker, a stimulation electrode 1 and a stimulation pulse generator supplying the stimulation electrode 1 are provided. Furthermore an ECG amplifier 2 is connected on the one hand to the stimulation electrode 1 and on the other hand to a detection stage for detecting the stim-T interval as a measuring variable. Moreover such a system contains a microprocessor, which can be programmed via a telemetry 25 stage 12, with a process control 11.

The functional blocks of the frequency control system are an HRmax/HRmin memory 7 to store the limit values of the stimulation frequency, a control stage 8 connected to the memory, to which stage a control variable ΔERG is supplied, a stimulation interval modulator 9 to fix

and modulate the stimulation interval and which is connected to the stimulation pulse generator 10.   Furthermore a calculation stage 4 is provided which receives a signal from the detection stage 3 and from the modulator 9, and a stage 5 to form the [median] average value, a set value

5   memory 6 and a set/actual value comparator 13.

The functioning of the cardiac pacemaker is as follows. 5 The stimulation pulse generator 10 supplies a stimulation pulse to the stimulation electrode and the ECG amplifier amplifies the intracardial ECG signal derived via the stimulation electrode 1.   From this amplified signal, the

10   detection stage 3 analyses the interval duration STI between the stimulation pulse and the T wave which corresponds to the QT interval or the action potential duration. In the calculation stage 4, the gradient of the electric restitution ERG is calculated, however others of the above-mentioned variables can also be used.   To this end first of all, triggered by the

15   modulator 9, the change $\pm\Delta$STI is calculated, with the stim-T interval value supplied by the detection stage, which change has been caused by the change ΔESI in the stimulation interval, and then the quotient ERG = ΔSTI/ΔESI is determined. In the median value stage 5, the median value ERGm of the ERG values is calculated over a plurality of change cycles.

20   With the arrow from the exit of the median value stage 5 to the set value memory 6 is indicated that the ERGm value, which in the body's rest state is measured at a median stimulation frequency of roughly 90/min, is stored as the set value.

In the set Value/actual Value Comparator 13, the difference between the median value of the gradient of the electric restitution ERGm and the set value ERGs is formed, and is given as the difference value ΔERG to the control stage 8, the latter being used to adjust the median stimulation frequency HR_0. This is calculated for example with the aid of the following functions:

HRo = HRmin + k*ΔERG,

wherein HR is so regulated that HR is < HRmax. Here HRmin and HRmax are minimum or maximum frequencies which can be predetermined by external programming and stored in the memory 7, and k is a proportionality factor. HRmin is generally predetermined by the optimum median stimulation frequency HRo in the rest state. The basic frequency HRo thus determined is supplied to the modulation stage 9, in which the basic cycle length BOL = 1/HRo is modulated periodically with an interval change ±AESI and the resulting stimulation interval ESI = BCLo + ΔESI is formed. In the following stimulation pulse generator 10, the stimulation pulse is then output in dependence on the ESI value. The regulation is repeated until the value ΔERG is zero.

In the above-described value, as the set value for the gradient of the electric restitution ERGs, the level was selected which arises for the individual load curves according to Fig. 2 at the optimum stimulation frequency HRo, control fluctuations between the values ERGi and ERG2 being admitted. The set value ERGs can however also be automatically

adapted to longer-term fluctuations of the restitution gradient with the aid of a second measuring parameter, independent of the modulation, with which parameter it is possible to [recognise] recognize the rest state of the patient. In the rest phase then the minimum stimulation rate HRmin is automatically

5   adjusted and the set value ERGs is adapted to the restitution gradient measured at rest. In this manner, the set value is "recalibrated". The measuring parameter which is independent of the modulation can be supplied for example by a mechanical movement sensor. The set value can also be adjusted in dependence on the frequency, for example it can be fixed

10   during the rest state and then provided with a frequency-dependent slope.

Although modifications and changes may be suggested by those skilled in the art, it is the intention of the inventors to embody within the patent warranted hereon all changes and modifications as reasonably and properly come within the scope of their contribution to the art.

PCT/EP99/09756

St. Jude Medical AB

99P2001P

uee title from
Pre-eAmdt !

The Invention relates to a cardiac pacemaker in ac-
cordance with the preamble of the main claim.

5

A generally known cardiac pacemaker is the so-called
QT-or stimulus-T pacemaker such as is described for
example in US 422 8 803. Such a pacemaker has means
with which the median stimulation frequency can be
10   adapted to changes in physical and psychic stress.

To this end a circuit is provided which evaluates the
ECG signal derived intracardially, detecting the be-
ginning or the maximum of the T wave. Since the time
15   interval between stimulation and the start of the T
wave, the so-called stim-T interval shortens with in-
creasing stress, the circuit delivers a physiological
measuring parameter with which the stimulation fre-
quency can be adapted to changing stresses.

20

The principle disadvantage of a frequency control
system of this kind is given in that the stim—T
interval does not shorten only with an increase in
stress but to a considerably greater degree through
the rise of the stimulation frequency itself.
Frequency control of this type correspondingly
requires special measures in order to avoid positive
feedback.

A further disadvantage of this system of frequency
control is the fact that the measured stim—T intervals
are determined from humours i.e. react on the basis of
the hormones poured out via the adrenal cortex and
transported via the blood circulation.

In principle, in the regulation of the stimulation
frequency in cardiac pacemakers it is an essential
goal to adapt the stimulation frequency not only to
rising physical stresses, but in so doing also to take
into account the individual myocardial capacity of the
patient. This means that the stimulation frequency is
only increased with rising stress as long as thereby
a rise in the heart time volume (HTV) is achieved.
This is intended to prevent the myocardium from being
overloaded and damaged by too high a stimulation
frequency ("overpacing")

An attempt has been made to achieve this control by
measuring the beat volume BV or an HTV-dependent
measuring parameter, such as for example the central
venous oxygenation (s02)

From WO 89/06990 is known a method for haemodynamic
optimisation of the stimulation frequency, which uses
the measurement of the central venous oxygenation s02,
dependent on the heart time volume, in combination
with a modulation of the stimulation frequency ΔHR
over phases of two to four minutes. Optimisation of

the heart time volume is aimed at in that the frequency—dependent gradient of the oxygenation AsO2/ΔHR is kept within a predetermined range, which is a physiologically optimum range analogous to the gradient of the heart time volume HTV/ΔHR.

This method depends on the stability and the accuracy of the s02 sensor catheter, which in practice have not proved to be sufficient, and the method has the disadvantage that on account of the necessary long change periods it is not possible in the necessary time of a few minutes to differentiate whether the measured s02 change is caused by the frequency change or by other influencing variables.

EP 0 551 355 describes a method for modulating individual stimulation intervals in which the impedance measurement is used to detect the beat volume, in order to avoid the use of a sensor catheter to determine the heart time volume. Through the deliberate modulation of individual stimulation intervals ΔSI and the phase- specific demodulation of the impedance change ΔZ, an attempt was made to suppress the influence of non- function-specific and thus disturbing parameter changes, and in addition the signal was calibrated with the aid of maximum modulation.

This method has the disadvantage that the principle of modulating individual stimulation intervals here is only used as a filtering and calibration method, i.e. as an interim step to determine the beat volume and thus the heart time volume (HTV). Optimisation of the frequency control is then also aimed at by the optimisation of the gradient ΔHTV/ΔHR on the basis of an optimum haemodynamic characteristic curve. The determination of the beat volume, despite an improvement in the signal—to-noise-ratio as a result

of the individual pulse modulation, has in practice
still proved too inaccurate to be able to carry out
reliable haemodynamic optimisation. This means that
optimisation of the stimulation by controlling the

5   heart time volume presents itself in practice as
problematic, since either the specific sensor
catheters for measuring the beat volume or the
HTV—dependent measuring parameters still have no
adequate long—term stability, or measurements of the

10 beat volume using standard catheters via the impedance
are not sufficiently reliable. Moreover the evaluation
becomes very complex since the mechanical transmission
functions also detected and which falsify the
measuring result must also be taken into account.

15

The object underlying the invention is to create a
cardiac pacemaker which renders possible quick and
accurate regulation of the stimulation frequency or
respectively of the duration of the stimulation

20 interval, and overloading by too high a stimulation
frequency is avoided.

This object is accomplished according to the invention
by the features of the main claim.

25

The cardiac pacemaker according to the invention which
has an individually optimised regulation of the
duration of the stimulation interval, avoids the
necessity of determining a BV- or HTV-dependent
measuring parameter and makes possible, through
evaluation of the electric restitution or of the
gradient of the electric restitution with the aid of
the standard detection of the endocardiac FOG, a
regulation of the stimulation frequency or of the
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function parameter of the heart, which directly
reproduces the stress state of the patient, changes in
the capacity of the myocardium and acute worsening of

myocardial performance being taken into account in the frequency adaptation. Here the modulation of individual stimulation intervals is carried out in such a way that the median adjusted interval duration does not alter.

Through the measures quoted in the subordinate claims, advantageous developments and improvements are possible.

The modulation of the stimulation intervals by a positive value and a negative value is carried out both continuously and also at an interval of a plurality of pulses with periodic repetition.

It was found that the electric restitution curve which is determined by measuring the duration of action potential, is equivalent to that which is defined by measuring the QT or the stim-T interval of the electrocardiogram.

Furthermore it has been shown that the analysis of the load- and frequency-dependent modulation of the stim-T interval is sufficiently reliable if the modulation of an individual stimulation interval gives the 20inequations ESI (Extrasystolic Interval) <600ms with ΔESI/BCL $\geq$ 10% (BCL = basic cycle length).

As the evaluation variable of the electric restitution, advantageously a dimensionless variable e.g. the gradient (ERG) or the relative change in the electric restitution can be used in order to achieve load- dependent control. This is possible since this gradient coincides with the rise in the physical load, whilst it rises with increasing stimulation frequency. Moreover it was also found that the change reaction is based mainly on a change in the time constants of the exponential restitution function and this time

constant reacts substantially more quickly and more strongly to changes in the load and the frequency than does the stim-T interval in a control system according to prior art.

Furthermore the control system according to the invention can be used well in cases of acute ischemia since the electric restitution reflects the myocardial conditions. The time constant of the exponential electric restitution, and also the gradient of same, rises with the ischemia. According to the invention this causes a reduction in the stimulation frequency.

The control system according to the invention using a single pulse modulation and detection of the electric restitution causes a quick and accurate regulation of the stimulation frequency, since the electric restitution is controlled mainly by a quick reaction mechanism controlled by neurons.

An embodiment of the invention is represented in the drawing and is described in greater detail in the following description.

The figures show:

Fig. 1   the characteristic course of an electric restitution curve of a normal healthy myocardium for the rest and for the load phase,

Fig. 2   characteristic curves for the electric restitution gradient as a function of the stimulation frequency in the rest phase and the load phase,

Fig.3   characteristic curves of the gradient of the electric restitution independence on

the stimulation frequency on occurrence of
an ischemia and

Fig. 4   a block diagram of an embodiment of the
           cardiac pacemaker according to the present
           invention.

The dependence of the duration of the action potential
AP of the myocardium as a function parameter of the
duration of the diastole t_d is designated as electric
restitution. If this is spontaneously changed during
a single heart cycle, for example through an
extrasystole, then the action potential or its
duration changes. The duration of the action potential
is defined by the interval between the beginning of
the stimulation and the time at which the action
potential has sunk by 90%, and it decreases if the
time interval between two successive stimulation
pulses becomes smaller. Here a distinction is to be
made between the APD change after an extrasystolic
stimulation interval and the APD change after a change
in the median or basic heart frequency (HR = 1 BCL)
according to prior art. This alteration behaviour
after an extrasystolic stimulation interval can be
described by a double exponential function which is
referred to as the electric restitution curve ER.

The electric restitution curve (ERC) is thus defined
as a function of the action potential duration APD
of the cycle length of a previous extrasystolic
stimulation pulse interval ESI, i.e. of an individual
stimulation pulse interval which is changed from the
basic cycle length (BCL), i.e. the median stimulation
interval duration by ±ΔESI, and which corresponds to
the diastole.

The function can be described as

ER APD(ESI) = $APD_{Pl}*(1-A1*\exp(-td/T1)-A2*\exp(-t_d/T2))$.

Herein, APD_{Pl} is the plateau value, A1 and T1 are the amplitude and time constant of the quick phase of the
5   restitution and A2 and T2 are the amplitude and time constant of the slow phase of the restitution.

The distinction in the approximate equation between a slow and a quick portion in the exponential rise of
10 the restitution curve takes into account the fact that functions of the myocardium or of the myocardial cell are determined at the cell membrane like the ion exchange, i.e. both through quick autonomous regulating processes in the cell and the surrounding
15 tissue and also through regulating processes which affect the whole heart— cardiovascular system and are controlled by the vegetative nervous system and the corresponding gland functions.
As a measuring parameter to determine the electric
20 restitution curve, as indicated above, in principle the action potential duration APD is determined which can be measured by special electrodes. Tests have shown however that in measuring the ECG also the so-called QT interval, i.e. the duration of the interval
25 between the Q peak and the end of the T wave of the intracardial ECG has the same restitution characteristic as the APD. On stimulating the ventricle with a cardiac pacemaker 25 it is more expedient to measure, instead of the QT interval as
30 the measuring interval, the stim—T interval STI, i.e. the interval between stimulation pulse and T wave.

In Fig. 1 is represented as the electrical restitution
30 curve (continuous line) the course of the action potential duration APD in dependence on the length of individual extrasystolic intervals of a normal healthy myocardium for the rest phase and for a load phase. Here in both phases respectively the optimum adapted

stimulation frequency HRo or the optimum basic cycle length BCLo = 1/HRo (i.e. the median duration of the stimulation interval) was changed in individual extrasystolic stimulation intervals ESI and then the

5 corresponding change in the action potential duration APD measured. The restitution curves thus produced correspond to the exponential functions described by the above equation. The optimum basic cycle length BCLo for rest (90 ins) and for a load (500 ins) are

10 represented by the broken arrows, i.e. the respective basic cycle length or median interval duration was altered by $\pm\Delta$ESI to form extrasystolic intervals, and respectively as the reaction the action potential duration or the QT- or stim-T interval was measured as

15 the measuring parameter. Here mean durations of the stimulation interval were alternately so shortened and prolonged by positive and negative ΔESI values that the adjusted median interval duration remains the same. Preferably the $\pm\Delta$ESI remains the same during a

20 change, i.e. the interval duration is shortened and prolonged by the same value. The change can be repeated periodically at an interval of a plurality pulses, however it can also be carried out continuously, i.e. each stimulation pulse is

25 alternately shortened or prolonged. The broken lines in Fig. 1 represent the curves of the QT or stim-T intervals of an ECG with continuous alteration of the basic cycle length, or respectively with continuous modulation, which is used for example in a QT

30 pacemaker according to prior art. As can be recognised, these characteristic curves are clearly different from the electric restitution curves with a differing load, and with increasing load, in addition to a reduction of the plateau value of the respective

35 curve with a corresponding displacement to the left also a steeper rise in the curve was measured.

The restitution curve can now be used for physiological control of the stimulation frequency HR, it being essential, as mentioned, that both the plateau value APD_{pl} and the time constants Tl and T2

5   are dependent on the pulse frequency HR and the level of myocardial efficiency. The stimulation frequency should therefore be so adjusted that the stimulation interval lies in the region of the plateau value APD_{pl} with any load.

10

In order to be able to use a simpler variable for the 10 regulation, advantageously not directly the region around the plateau value itself is selected but the gradient of the restitution curve. The gradient of the

15   restitution curve in the respective optimum operating point, which is given by the optimum basic cycle length BCLo arises in that the extrasystolic interval ESI is altered as a percentage ($\Delta ESI/BCL$) by a defined positive $+\Delta ESI$ and/or negative value $-\Delta ESI$ and the

20   resulting change in the action potential duration $+\Delta APD$ or $-\Delta APD$, shown by arrows 20 in Fig. 1, is measured.   If this gradient of the electric restitution ERG =

25    $+\Delta APD/+\Delta ESI$ or ERG = $-\Delta APD/-\Delta ESI$ is applied as a function of the stimulation frequency HR for the rest phase and a load phase, the course represented in Fig. 2 arises.

Fig. 2 shows that the exponential rise of the gradient of the electric restitution ERG as a function of a rising stimulation frequency HR with rising load is displaced to the right. It can be recognised that in the respective optimum heart frequency, the associated ERG_{0} values, which correspond to the plateau values APD_{pl} in Fig. 1, have approximately the same level, however the values can also be different. These values can be selected in a frequency control system as set

values of the gradient of the electric restitution
ERG, a region around the set value ERG being given in
Fig. 2 as a range for an optimum stimulation frequency
HR, which is delimited by the threshold values ERG1
5   and ERG2.

It is also conceivable that the gradient of the
electric restitution ERG is determined from the
difference between the positive and negative changes
10   in the action potential duration in relation to the
positive and negative interval changes, namely with
ERG = $[(+\Delta APD)-(-\Delta APD)]/[(+\Delta ESI)-(-\Delta ESI)]$.

On the basis of Figs. 1 and 2 it can be recognised
15   that the electric restitution function or its gradient
ERG offers the precondition for regulating the
stimulation frequency since on the one hand the
gradient of the electric restitution ERG reacts with
an increase in the stimulation frequency conversely to
20   the rise in the physical stress and on the other hand
has within a physiologically fixed defined region an
optimum value ERGo for each stress situation. From the
ERG characteristic curve according to Fig. 2 it can be
recognised that in the frequency control too high a
25   stimulation frequency (overpacing) is avoided in
principle.

However it is also apparent that a possible acute
worsening in myocardial performance in patients can be
recognized and can be taken into account in the
adaptation of the frequency. In Fig. 3 is represented
the gradient of the electric restitution via the
stimulation frequency for a case in which a worsening
of the myocardial performance occurs through ischemia.
Fig. 3 shows that the lengthening of the stim-T
interval on the occurrence of an ischemia displaces
the ERG curve to the left in a case of stress, i.e.
the gradient of the electric restitution reacts on a

drop in the myocardial capacity as in a drop in physical stress. As a result of this, the optimum stimulation frequency PRo is reduced and thus the pre—eminent requirement is met that the ERG-dependent

5   frequency control system prevents overpacing in a myocardium which is deteriorating pathologically.

In another example, instead of the gradient, the relative change in the electric restitution can be

10   used by forming the quotient $\Delta APD/\Delta ESI$, in each case also the median values being able to be determined over a plurality of change cycles.

In Fig. 4 is represented an embodiment of a cardiac

15   pacemaker, with which frequency control is used in dependence on the gradients of the electric restitution function ERG.

The functional blocks required for controlling

20   frequency or the stimulation interval in dependence on the ERG are represented in the bordered area. As other functional blocks, which form part of the standard equipment of a normal QT pacemaker, a stimulation electrode 1 and a stimulation pulse generator

25   supplying the stimulation electrode 1 are provided. Furthermore an ECG amplifier 2 is connected on the one hand to the stimulation electrode 1 and on the other hand to a detection stage for detecting the stim-T interval as a measuring variable. Moreover such a

30   system contains a microprocessor, which can be programmed via a telemetry stage 12, with a process control 11.

The functional blocks of the frequency control system are an HRmax/HRmin memory 7 to store the limit values of the stimulation frequency, a control stage 8 connected to the memory, to which stage a control variable ΔERG is supplied, a stimulation interval

modulator 9 to fix and modulate the stimulation interval and which is connected to the stimulation pulse generator 10. Furthermore a calculation stage 4 is provided which receives a signal from the detection

5 stage 3 and from the modulator 9, and a stage 5 to form the median value, a set value memory 6 and a set/actual value comparator 13.

The functioning of the cardiac pacemaker is as

10 follows. 5 The stimulation pulse generator 10 supplies a stimulation pulse to the stimulation electrode and the ECG amplifier amplifies the intracardial ECG signal derived via the stimulation electrode 1. From this amplified signal, the detection stage 3 analyses

15 the interval duration STI between the stimulation pulse and the T wave which corresponds to the QT interval or the action potential duration. In the calculation stage 4, the gradient of the electric restitution ERG is calculated, however others of the

20 above—mentioned variables can also be used. To this end first of all, triggered by the modulator 9, the change $\pm \Delta STI$ is calculated, with the stim—T interval value supplied by the detection stage, which change has been caused by the change ΔESI in the stimulation

25 interval, and then the quotient $ERG = \Delta STI/\Delta ESI$ is determined. In the median value stage 5, the median value ERGm of the ERG values is calculated over a plurality of change cycles. With the arrow from the exit of the median value stage 5 to the set value

30 memory 6 is indicated that the ERGm value, which in the body's rest state is measured at a median stimulation frequency of roughly 90/min, is stored as the set value.

In the set value/actual Value comparator 13, the difference between the median value of the gradient of the electric restitution ERGm and the set value ERGs is formed, and is given as the difference value ΔERG

to the control stage 8, the latter being used to adjust the median stimulation frequency HRp. This is calculated for example with the aid of the following functions:

5

$$HRo = HRmin + k*\Delta ERG,$$

wherein HR is so regulated that HR is < HRmax. Here HRmin and HRmax are minimum or maximum frequencies
10 which can be predetermined by external programming and stored in the memory 7, and k is a proportionality factor. HRmin is generally predetermined by the optimum median stimulation frequency HRo in the rest state. The basic frequency HRo thus determined is
15 supplied to the modulation stage 9, in which the basic cycle length BOL = 1/HRo is modulated periodically with an interval change $\pm\Delta ESI$ and the resulting stimulation interval ESI = BCLo + ΔESI is formed. In the following stimulation pulse generator 10, the
20 stimulation pulse is then output in dependence on the ESI value. The regulation is repeated until the value ΔERG is zero.

In the above-described value, as the set value for the gradient of the electric restitution ERGs, the level was selected which arises for the individual load curves according to Fig. 2 at the optimum stimulation frequency HRo, control fluctuations between the values ERG1 and ERG2 being admitted. The set value ERGs can however also be automatically adapted to longer-term fluctuations of the restitution gradient with the aid of a second measuring parameter, independent of the modulation, with which parameter it is possible to recognise the rest state of the patient. In the rest phase then the minimum stimulation rate HRmin is automatically adjusted and the set value ERGs is adapted to the restitution gradient measured at rest. In this manner, the set value is "recalibrated". The

measuring parameter which is independent of the
modulation can be supplied for example by a mechanical
movement sensor. The set value can also be adjusted in
dependence on the frequency, for example it can be
fixed during the rest state and then provided with a
frequency-dependent slope.

Patent Claims

1.   Cardiac pacemaker comprising a device for
producing successive stimulation pulses of a median
duration of the stimulation interval, a device for
modulating individual stimulation intervals (ESI) and
a device for detecting a cardiac function parameter
and for evaluating the changes in the cardiac function
parameter caused by said modulation, the stimulation
interval duration being altered in dependence on the
evaluated cardiac function parameter, **characterised in
that**
the device for modulating the stimulation intervals
(551) alternately shortens and prolongs the
stimulation intervals in such a way that the
respective adjusted median stimulation interval
duration does not change and the evaluation device
determines the electric restitution of the heart at
this median stimulation interval duration on the basis
of the measurement of the duration of the action
potential, the changes in a measuring variable of the
duration of the action potential caused by the
modulation of individual stimulation intervals being
determined in relation to that in the median duration
of the stimulation interval and being compared with at
least one set value (ERGs), and in that the median
duration of the stimulation interval is controlled on
the basis of said comparison.

2.   Cardiac pacemaker according to claim 1,
characterised in that the device for modulating

individual stimulation intervals (ESI)carries out the alternating change repeating it periodically at intervals of a plurality of pulses.

3.   Cardiac pacemaker according to claim 1, **characterised in that** the device for modulating individual stimulation intervals (ESI) carries out the alternating change ($-\Delta$ESI, $+\Delta$ESI) continuously.

4. Cardiac pacemaker according to one of claims 1 to 3, **characterised in that,** as the measuring variable for determining the electric restitution, the duration of the action potential (APD) of the myocardium or the time interval between the stimulation pulse and the T wave in the ECG(ST) or the QRS complex and T wave in the ECG(QT) is used.

5. Cardiac pacemaker according to one of claims 1 to 4, **characterised in that** the median value of the measuring variable (APDm, STm or QTm) determining the electric restitution is calculated over a plurality of stimulation intervals.

6. Cardiac pacemaker according to one of claims 1 to 5, **characterised in that** the changes, dependent on the respective change in the stimulation interval (AESI), of the measuring variable determining the electric restitution are stored and in that their median value (ΔAPDm or ΔSTm or ΔQTm) is determined over a plurality of change cycles.

7. Cardiac pacemaker according to one of claims 1 to 6, **characterised in that**, to evaluate the change in the measuring variable, a dimensionless variable of the 25 electric restitution is used.

8.   Cardiac pacemaker according to claim 7, **characterised in that,** as the dimensionless variable of the electric restitution, the gradient of the electric restitution (ERG) is calculated by forming the quotient $\Delta APD/\Delta ESI$ or $\Delta STm/\Delta ESI$ or $\Delta QTIm/\Delta ESI$, or the relative change in the electric restitution by forming the quotient $\Delta APDm/APDm$ or $\Delta STm/STm$ or $\Delta QTm/QTm$.

9.   Cardiac pacemaker according to claim 1 to 8, **characterised in that** the set value(ERGs) is predetermined by the value of the gradient or of the relative change in the electric restitution in the 5 body's state of rest.

10.   Cardiac pacemaker according to claim 5, **characterised in that,** in order to adapt the set value (ERGs) to individual fluctuations in the electric restitution, the median duration of the stimulation interval is fixed by external programming in the patient's state of rest and the value measured in this rest phase is stored as an absolute set value (ERGs).

11.   Cardiac pacemaker according to claim 9, **characterised in that,** in order to adapt the set value 15 (ERGs) to longer-term fluctuations of the electric restitution, the rest state of the patient is recognised by means of a sensor and the median duration of the stimulation interval is adjusted and the stored set value (ERGs) is replaced by the value measured in the detected rest phase.

12.   Cardiac pacemaker according to one of claims 1 to 9, **characterised in that,** to compensate for the frequency-dependent changes in the detection of the T waves, the set value (ERGs) is altered in dependence on 25 the duration of the stimulation interval.

13. Cardiac pacemaker according to one of claims 1 to 8, **characterised in that** the median duration of the stimulation interval is controlled in such a way that it rises if the difference between the restitution 30 gradient and the set value falls below a negative threshold value and drops if the difference exceeds a positive threshold value.

5
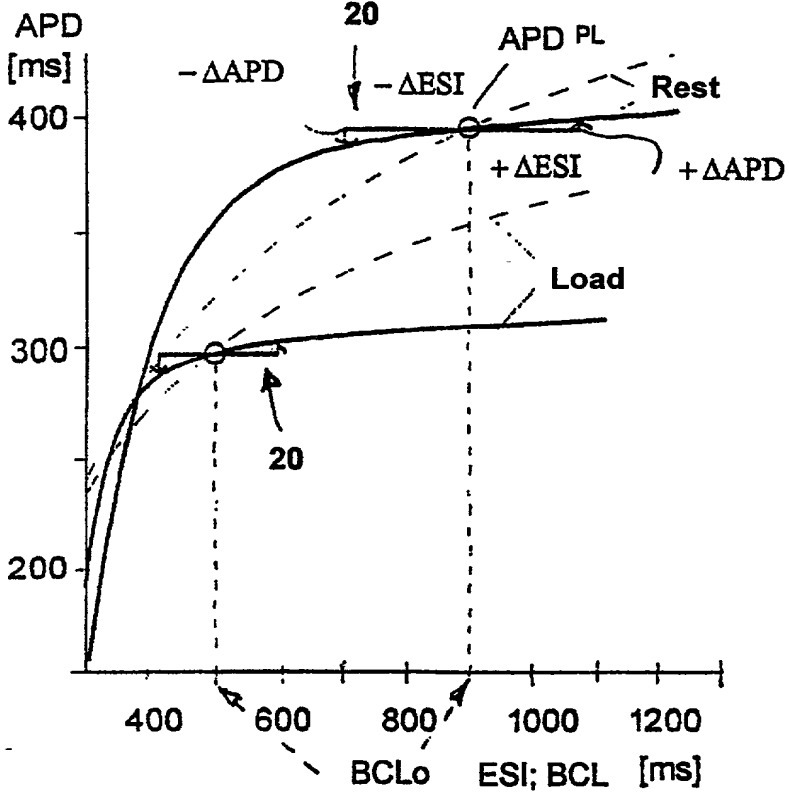
Fig. 1
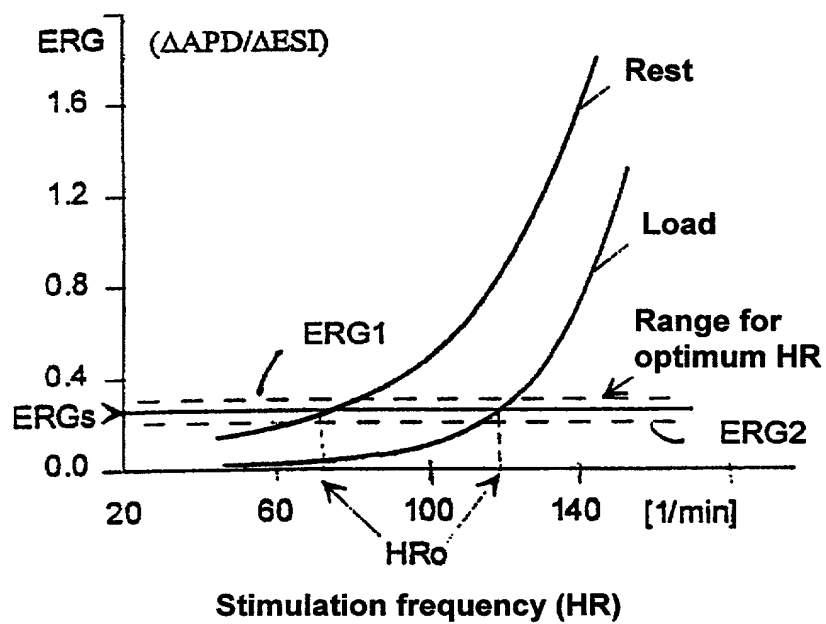
Fig. 2
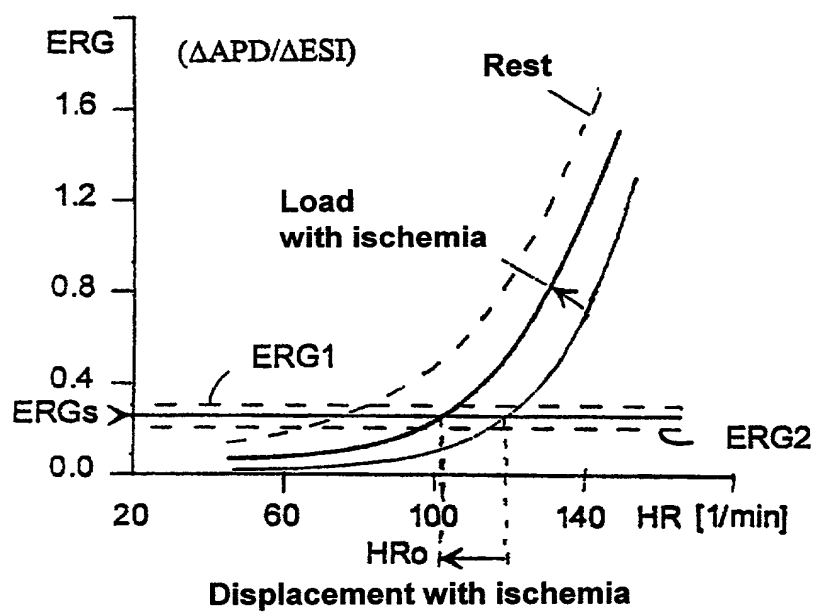
Fig. 3
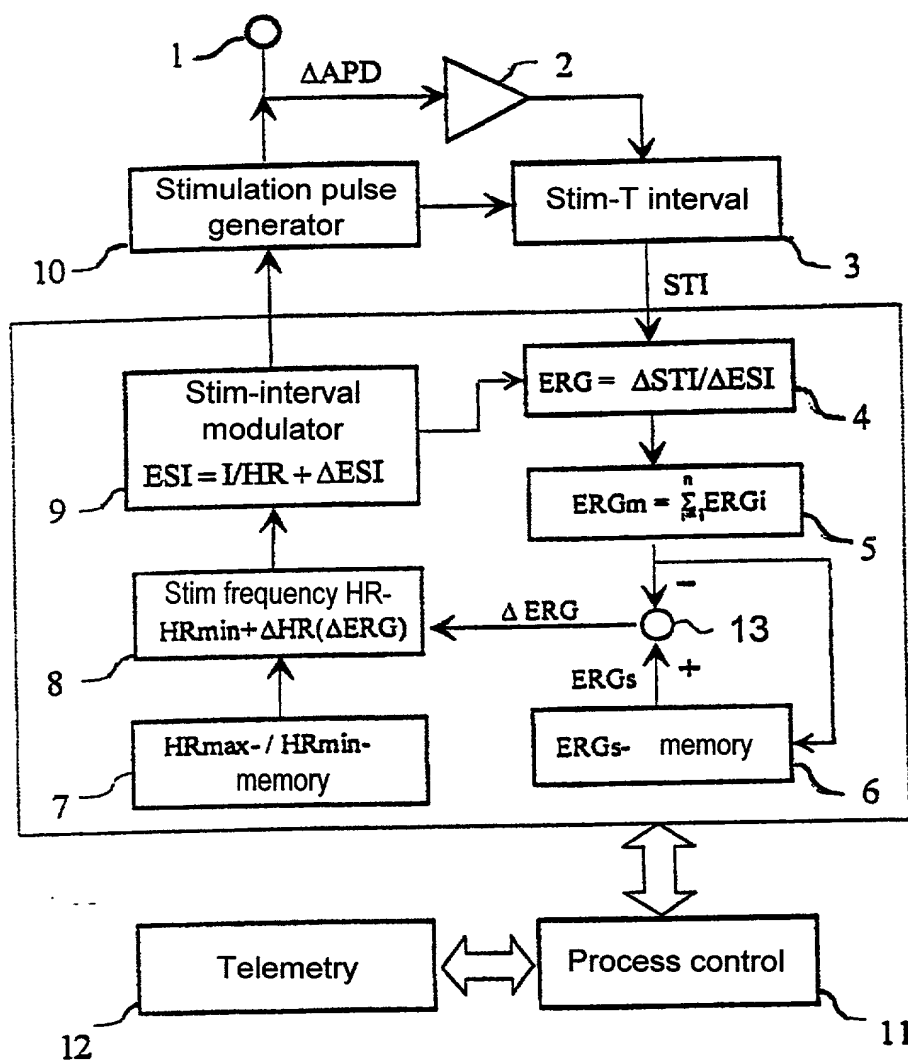
Fig. 4

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PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

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PCT APPLICATION NO	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected herewith.

And I hereby appoint all Attorneys identified by the United States Patent & Trademark Office Customer Number 26574, who are all members of the firm of Schiff, Hardin & Waite.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DATE 28.06.01	DATE 28.06.01	DATE

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER P01,0235

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

the specification of which (check only one item below):

- ☐ is attached hereto.

- ☐ was filed as United States application
  Serial No. _____

  on _____,

  and was amended

  on _____ (if applicable).

- ■ was filed as PCT international application

  Number _____ PCT/EP99/09756 _____

  on _____ November 30, 1999 _____,

  and was amended under PCT Article 19

  on _____ (if applicable).

I hereby state that I have reviewed and understand the contest of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
Germany	199 00 690.3	05.01.99	■ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO